Summary Minutes of the
Arthritis Advisory Committee
September 16, 2009
Location: Holiday Inn, The Ballrooms, Two Montgomery Village Avenue,
Gaithersburg, Maryland

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the September 16, 2009 Meeting of the Arthritis Advisory Committee of the Food and Drug Administration were approved on __10/16/2009_____.

I certify that I attended the September 16, 2009 meeting of the Arthritis Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

__/s/_____ Nicole Vesely, Pharm.D.
Designated Federal Official, AAC

_____/s/_____ Kathleen O'Neil, M.D.
Committee Chair

The Arthritis Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on September 16, 2009 at the Holiday Inn, The Ballrooms, Two Montgomery Village Avenue, Gaithersburg, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the sponsor. The meeting was called to order by Kathleen O'Neil, M.D. (Chair); and the conflict of interest statement was read into the record by Nicole Vesely, Pharm.D. (Designated Federal Official). There were approximately 110 persons in attendance. There were six speakers for the Open Public Hearing session.

Issue: The committee discussed biologics license application (BLA) 125338, Xiaflex (collagenase clostridium histolyticum), sponsored by Auxilium Pharmaceuticals, Inc., for the proposed treatment of advanced Dupuytren's disease. Dupuytren's disease is a condition in which the tendons of the hand that help move the fingers of the hand become thickened and scarred.

Attendance:

Arthritis Advisory Committee Members Present (Voting):
Diane Aronson (Consumer Representative), Lenore Buckley, M.D., M.P.H , Nancy Olsen, M.D., Kathleen O'Neil, M.D. (Chair), Kenneth Saag, M.D.

Special Government Employee Consultants (Temporary Voting Members):
William Brackney (Patient Representative), Mustafa Haque, M.D., Saul Kaplan, M.D., Kathleen Mazor, Ed.D., Timothy McAlindon, M.D., M.P.H., M.R.C.P., William Swartz, M.D., F.A.C.S., Michael Weisman, M.D.

Arthritis Advisory Committee Members Not Present:
David Blumenthal, M.D.
Mark Fletcher, M.D. (Industry Representative)
Robert Kerns, Ph.D.
Gail Kerr, M.D.
Ted Mikuls, M.D., M.S.P.H.
Christy Sandborg, M.D.
Robert Stine, Ph.D.

FDA Participants (Non-Voting):
Curtis Rosebraugh, M.D., M.P.H., Bob Rappaport, M.D., Sarah Okada, M.D., Eric Brodsky, M.D., Kathryn O'Connell, M.D., Ph.D.

Designated Federal Official:
Nicole Vesely, Pharm.D.

Open Public Hearing Speakers:
Tom Fewell
Rodney Van Sickle
Karen Mercaldo
Kenneth C. Nelson
Bill Walker
Robert G. Hamilton, Ph.D., Johns Hopkins University

The agenda was as follows:

Call to Order Introduction of Committee	**Kathleen O'Neil, M.D.** Chair, AAC
Conflict of Interest Statement	**Nicole Vesely, Pharm.D.** Designated Federal Official
AAC Member Appreciation	**Bob Rappaport, M.D.** Director, Division of Anesthesia, Analgesia and Rheumatology Products, CDER/FDA
Opening Remarks	**Sarah Okada, M.D.** Clinical Team Leader, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP), CDER/FDA

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Sponsor Presentation	**Auxilium Pharmaceuticals, Inc.**
Introduction	**Benjamin Del Tito, Ph.D.** Senior Vice President, Quality and Regulatory Affairs Auxilium Pharmaceuticals, Inc.
Dupuytren's Disease and Current Management	**F. Thomas D. Kaplan, M.D.** Indiana Hand Center Clinical Associate Professor of Orthopedic Surgery Indiana University School of Medicine
AA4500 Clinical Efficacy	**Anthony DelConte, M.D.** Chief Medical Officer Auxilium Pharmaceuticals, Inc.
AA4500 Clinical Safety Risk Mgmt Activities	**James Tursi, M.D.** Vice President, Clinical Affairs Auxilium Pharmaceuticals, Inc.
Benefit/Risk Profile	**Anthony DelConte, M.D.**

Questions from the Committee to the Sponsor

FDA Presentation Collagenase clostridium histolyticum for the proposed treatment of advanced Dupuytren's disease	**BLA 125338** **Eric Brodsky, M.D.** Clinical Reviewer, DAARP, CDER/FDA
Risk Management Considerations in the FDA Approval Process	**Kathryn O'Connell, M.D., Ph.D.** Drug Risk Management Analyst, OSE/CDER/FDA

Questions from the Committee to the FDA

Open Public Hearing

Questions to the AAC and AAC Discussion

Adjourn

Questions to the committee:

1. **Investigator training in the clinical studies included injection technique instruction via manuals and DVDs, workshops, and investigator meetings. This may be more extensive than the training proposed for the education of healthcare professionals in clinical practice if the product is approved. Please discuss the adequacy of the proposed training.**

    - *Some members commented that a mandatory patient registry would be needed to monitor the safety of Xiaflex long term. Other members noted that a mandatory patient registry would restrict access and be unnecessarily burdensome.*

    - *Some members stated that other office procedures (e.g., injections for varicose veins, steroid injections of the hand for trigger fingers) do not require credentialing and access to these procedures are not restricted by the FDA.*

    - *Some members commented that the proposed training was not sufficient for many rheumatologists to perform the procedures. Other members disagreed and stated that the proposed training was adequate for rheumatologists or other medical specialists to inject Xiaflex.*

    - *Some committee members stated that voluntary registries in current use in the United States do not provide adequate information.*

    - *Members agreed that Xiaflex was beneficial in the treatment of Dupuytren's contracture and met an unmet need. Many members stated that the benefit/risk ratio was positive.*

    - *Some members commented that the proposed training to be provided was adequate for those clinicians who are knowledgeable of the anatomy of the hand and comfortable with performing injections in the hand. One member commented that it was necessary for the Sponsor to provide tutorials or models to demonstrate the procedure for administration and manipulation following the procedure to those physicians not familiar with the anatomy of the hand.*

    - *Some members commented that clinicians may not pay full attention to the training provided through the DVD and recommended that a check be put in place to ensure completion of the training process such as a requirement to pass a test.*

    - *Some members commented that it would be difficult to monitor Xiaflex-treated patients in the office setting as those that do well after treatment may not be willing to return for*

follow up visits. Other members stated that patients with serious complications (e.g., tendon ruptures) would not likely be lost to follow-up.

- *Members commented that a post marketing study would be helpful to address data gaps pertaining to efficacy and safety with a broader range of administering physicians, and to address questions of long-term efficacy (i.e. contracture recurrence) and safety (i.e. risks of hypersensitivity with repeated exposures over extended periods).*

- *Some members recommended that active data mining of Xiaflex-associated events in healthcare databases should be done.*

Please see the transcript for detailed discussion.

2. VOTE: In view of the data available for safety and efficacy, do you recommend approval of Auxilium's clostridial collagenase for the treatment of patients with advanced Dupuytren's Disease?

Vote : Yes=12 No = 0 Abstain = 0

- *Members agreed that Xiaflex was beneficial and the level of risk was acceptable.*

Please see the transcript for detailed discussion.

3. Depending on your response to Question 2, please address the following questions:

a. If you recommend approval, what additional studies, if any, should be conducted post-approval to further assess the safety of the product?

- *One member noted that a mandatory registry of patients may help determine whether the proposed physician training was adequate. Other members stated that any restriction on the use of Xiaflex including a mandatory patient registry would be onerous and the decision to inject Xiaflex should be left to each physician.*

- *Other members noted that they were opposed to a mandatory registry and felt that the necessary information could be gained through a Phase 4 post marketing study.*

- *A few members noted that a standardized national consent form should be developed to inform all patients of the risks of Xiaflex injection; however, others noted that this may not be feasible.*

- *One member was concerned about the clinical implications of high IgE titers following Xiaflex injections. There was also concern of the potential to cause serious allergic reactions with repeated use, something that has not been tested.*

Please see the transcript for detailed discussion.

b. If you do not recommend approval, what additional data are needed to support approval?

The committee did not address this question as approval was unanimously recommended.

The meeting adjourned at approximately 3:15 p.m.